Applicant acknowledges that his request for continued examination under 37 CFR1.114, including the fee set forth in 37 CFR 17(e), was accepted and that the finality of the previous Office action was withdrawn.

Applicant also acknowledges that claims 33-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention (see the previous Office Actions November 13, 2002 and February 12, 2002) and are the subject of a divisional application.

Applicant further acknowledges that claims 1-32 are being examined on the merits herein.

Applicant still further acknowledges that the declaration of Dr. Lenard M. Lichtenberger (inventor) submitted February 13, 2003, was entered into the file as Paper No. 17.

Claim Rejections* - 35 *USC* § *103

Claims 1-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over DAIFOTIS, et al. (WO 9904773, of record) in view of Lichtenberger et al. (5,763,422, of record), further in view of Hovancik et al. (5,869,471, of record).

The Examiner contends as follows:

> Daifotis et al. discloses that bisphosphonates such as atendronate, risedronate, tiludronate and ibandronate, within the instant claims, are known to be useful in pharmaceutical compositions and methods for treating osteoporosis. See abstract, page c 1 lines 14-15 and page 2 lines 1-15. Daifotis et al. also discloses that bisphosphonates are known to have low bioavailability from GI tract and therefore cause adverse GI effects. See abstract, page 1-3. Further, Daifotis et al. discloses that the purpose of the methods therein are for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the adverse GI effects (see abstract and page 7 lines 22-23 in particular). Daifotis et al. also discloses the effective amounts of bisphosphonates to be administered in the compositions therein for minimizing the adverse GI effects (see Examples at page 24-27).
>
> Daifotis et al. do not expressly disclose the employment of one zwitterionic phospholipid to reduce GI toxicity of brsphosphonate when administering at least one bisphosphonate in a pharmaceutical composition. The prior art does also not expressly disclose the effective amounts of active agents in the composition herein to be administered.
>
> Lichtenberger et al. disclose that zwitterionic phospholipids, within the instant claims, (see abstract, col. 3 lines 59-67, col. 10 lines 50-62, col.11 .lines 60-65) are capable of reducing GI irritating (adverse) effects and is therefore useful broadly in combining with many NSAID drugs (see Table I at col.4 lines 25-52) in pharmaceutical compositions since NSAID drugs may cause GI adverse effects, *e.g.*, inducing GI ulcers and bleeding. See also abstract and col.1-2. Lichtenberger et al. also disclose the effective amounts of zwitterionic phospholipids in the pharmaceutical compositions therein. See col.12 lines 12-34.
>
> Hovancik et al. discloses that the combination of NSAIDs and

bisphosphonates is useful in improving the therapeutic effect for treatfng arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7)

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine one zwitterionic phospholipid to reduce G1 toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition since zwitterionic phospholipids are known to be capable of reducing GI irritating (adverse) effects that caused by other drugs such as many NSAIDs according to Lichtenberger et al. Moreover, bisphosphonates such as alendronate, risedronate, tiludronate and ibandronate are known to cause adverse GI effects and the purpose of the method of Daifotis et al. is known to minimize the adverse GI effects induced by bisphosphonates. Further, the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and, zwitterionic phospholipids is also known to be useful in methods for treating bone disorders.

Therefore, one of ordinary skill in the art would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonate in a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate. Hence, the combined teachings of Daifotis and Lichtenberger Hovancik have provided the motivation of the instant invention.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts or ratio of zwitterionic phospholipid and a bisphosphonate in a composition because the effective amounts of zwitterionic phospholipid to the administered are known in the art. Moreover, the optimization of amounts of active agents to be administered is considered well within the skill of artisan, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch,* 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks and the declaration of Dr. Lenard M. Lichtenberger (inventor) submitted February 13, 2003 in Paper No. 17 under37CFR 1.132 with respect to this rejection of claims 1-32 made under 35 U.S.C. 103(a), of record stated in the Office Action dated November 13 ,2002 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for the following reasons.

Again, Applicant arguments that there is no motivation to combine because there is no reasonable expectation that their combination would be successful are not found persuasive. As Applicant admits, Daifotis et al. clearly teaches that bisphosphonates can cause adverse GI effects when ingested. Daifotis et al. also disclose that their invention relates to methods for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the occurrence of or potential for

adverse GI effects (see page 1 lines 11-13). Thus, the teachings of Daifotis et al. are seen to provide the motivation to make the present induced by bisphosphonates.

Moreover, zwitterionic phospholipids (within the instant claims) are known to be capable of reducing GI irritating (adverse effects) and are therefore useful broadly in combining with NSAID drugs in pharmaceutical compositions in order to reduce GI adverse effects, e.g., inducing GI ulcers and bleeding, caused by NSAID drugs, according to Lichtenberger et al. As discussed in the previous Office Action, one of ordinary skill in the art, therefore, would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonatein a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate with a reasonable expectation for success, absent evidence to the contrary.

Additionally, Hovancik et at. has been cited by the examiner primarily for its teachings of that the combination of NSAIDs and bisphosphonates is useful in improving the therapeutic effect for treating arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7), further supports the examiner's position, since that the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders. Thus, one of ordinary skill in the art would reasonably expect that the combination of bisphosphonates and zwitterionic phospholipids would be successful in treating bone disorders, the same disorders, absent evidence to the contrary.

Applicant's arguments regarding that "the motivation to combine these to references is derived exclusively from hindsight" have been considered but are not found persuasive. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

Therefore, as discussed above, motivation to combine the teachings of the prior art to make the present invention is seen and no improper hindsight is seen. The claimed invention is clearly obvious in view of the prior art.

Dr. Lichtenberger's declaration herein is ineffective to overcome the 103(a) rejection herein since it is not seen to provide clear and convincing evidence of nonobviousness or unexpected results for the combination herein over the prior art. The declaration merely presents the testing results of the reduction of hydrophobicity of DPPC monolayers on glass slides with two particular bisphosphonates, which is not seen to be factual data for unexpected results the claimed combination herein in reducing GI toxicity caused by bisphosphonates because no testing results *in vivo* and no zwitterionic phospholipids employed in the testing are presented.

Therefore, the declaration is insufficient to rebut the prima facie case herein. For the above stated reasons, said cfaims are properly reletted under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant assert that this invention solves the problem of GI toxicity that has plagued the

treatment of osteoporosis with bisphosphonates since their FDA approval starting in the 1990's. The present invention, instead of being an administration protocol solution, is a compositional solution. The need for this type of a compositional solution to the problem was exacerbated further by the frequent administration of both a bisphosphonate to treat osteoporosis and an NSAID to ameliorate inflammation and pain associated with arthritis or other bone degenerative disorders as well as the co-administration of NSAIDs for reducing risk of cardiovascular disease. The combination of these two pharmaceuticals has resulted in significantly increased risk of GI ulceration even when the NSAID is given intravenously and the bisphosphonate is given orally. Thus, the basic GI toxicity of bisphosphonates and of NSAIDs are significantly and synergistically increased when the drugs are taken in combination. Such drug interactions are unpredictable and often unavoidable because of the pervasive use of NSAIDs.

The present invention is a compositional fix to the problem. Not only does the compositional remedy the basic toxicity of bisphosphonates, it is also effective in more than halving the synergistic increase in GI toxicity of co-administered bisphosphonates and NSAIDs, an synergistic effect that is seen even when the bisphosphonate is given orally and the NSAID is given intravenously. See Figure 4 of this application and the Second Dr. Lichtenberger Declaration. The present invention not only solves the GI toxicity of bisphosphonates compositionally, but also significantly reduces the increased bisphosphonate toxicity induced by co-administration of NSAIDs. Thus, this compositional solution to the GI toxicity problem answers a long felt need in general bisphosphonate administration and also in the rapidly increasing bisphosphonate market, now plagued by the co-administration of NSAIDs.

Applicant also reasserts his objection to the Examiner's reasoning on the obviousness of the ability for a phospholipid to reduce the GI toxicity of a bisphosphonate. While it is true that phospholipids have been shown to be effective agents that when pre-associated with an NSAID can reduce the GI toxicity of the NSAID, such an observation does not support the general proposition, as the Examiner states, that phospholipids will work to lower GI toxicity and increase bio-availability for all drugs, especially drugs that are radically different compositionally from NSAIDs.

Dr. Lichtenberger has submitted data demonstrating the fact that bisphosphonates are highly competitive with phospholipids for a model hydrophobic membrane (subsequently submitted Declaration). Based on this data, an ordinary artisan one could well conclude that the combination of a phospholipid and a bisphosphonate would greatly increase the likelihood that the bisphosphonate would find its way to the stomach lining because phospholipids, being more

hydrophobic than the stomach fluids, have a high affinity for the stomach lining. Thus, an ordinary artisan could have well reasoned that a bisphosphonate-phospholipid combination may have resulted in increased GI toxicity by increasing the relative concentration of the bisphosphonates at the stomach lining. The fact, that the opposite occurred was only clear after the experiment was performed. Applicant is not suggesting that an ordinary artisan could not have suggested that bisphosphonate-phospholipid combination would reduce GI toxicity, but in the absence of actual data, either eventually would be mere speculation with each being possible *ab initio*. Just like any civil court proceeding, prior to a judgment either party can when, only after the judgment is handed down does the winner become obvious. Thus, **only** in hindsight can one now claim that the latter theory was correct and the former theory incorrect, such is the world of science.

Turning to the cited references, Daifotis et al. is a dosing fix to the problem of GI toxicity, and not a fix to the underlying chemical causes of bisphosphonate GI toxicity. The problem with administrative protocol solutions to an adverse drug problem is that it requires cooperation from the patient to successfully implement the solution. This administrative fix is further complicated by the significantly adverse synergistic enhancement of bisphosphonate GI toxicity when an NSAID is taken during bisphosphonate administration. Nowhere in Daifotis et al. is there a suggestion that a compositional solution to bisphosphonate GI toxicity is possible. In fact, a fair reading of Daifotis et al. is that there is simply no need for any other solution to the problem, because a simply administration protocol can eliminate all GI toxic effects of bisphosphonates. Thus, there is simply no suggestion for combining Daifotis et al. with any Lichtenberger reference relating to phospholipid-NSAID compositions. When no problem exist, no one is looking to solve the problem. One of ordinary skill in the art would clearly view Daifotis et al. as providing a disincentive to look for any other solution to the problem of GI toxicity associated with bisphosphonate – Daifotis et al. claims to have a solution based on a simple administrative protocol.

The addition of Hovancik et al. further confusions, makes the obviousness argument less strong, and renders the obviousness argument even less tenable, because the unexpected consequence of co-administering an NSAID and a bisphophonate results in a significant and synergistic increase in the very problem that the present invention is designed to solve. As shown in data from Dr. Lichtenberger's lab set forth in a Second Dr. Lichtenberger Declaration, the co-administration of orally administered bisphosphonate and intravenously administered NSAID demonstrates a dangerous synergistic increase in GI toxicity of bisphosphonates. Thus, the predictability of pharmaceutical compositions is absolutely unpredictable regardless of the state of

the art knowledge at the time. The data in the attached figure shows that one bisphosphonate had little toxicity and the NSAID had moderate, but when co-administered by different administration pathways, the mixture had a GI toxicity 10 or more times higher for the bisphosphonate and several time higher for the NSAID when taken separately.

Applicant, therefore, believes that the combination of Daifotis et al. and any Lichtenberger NSAID reference does not render the present invention obvious because the Daifotis et al. does not support the combination and neither does the Lichtenberger references. These references simply do not suggest combining the teaching nor do they suggest that outcome of the combination. In fact, Daifotis et al. can be fairly read as teaching squarely away from such a combination. Daifotis et al. states and claims a cure to the basic problem the Examiner now believes Daifotis et al. suggest should be cured by adding a phospholipid, but this contention flies fully in the face of the Daifotis et al. teaching – ordinary artisan look no farther for we have eliminated this problem. Such a statement teaches squarely away from the present invention – the problem is solved.

Applicant, therefore, respectfully requests withdrawal of this rejection as one of ordinary skill in the art would fairly view Daifotis et al. as teaching away from solving a solved problem, a problem Daifotis et al. indeed claims to have solved. Moreover, the combination of all three references does not suggest the combination and in fact the inclusion of Hovancik et al. further demonstrate the total unpredictability of drug combinations.

Applicant has also added new claims 46-48 which add the additional limitation that the two components are in their zwitterionic form. Nothing in Daifotis et al. suggests anything associated with phospholipids and further does not suggest that both compounds be in their zwitterionic form in the composition prior to administration. Applicant therefore request allowance of these new claims.

The Commissioner is authorized to charge any additional fees or credit any overpayments to Deposit Account No. 501518.

If it would be of assistance in resolving any issues in this application, the Examiner is kindly invited to contact applicant's attorney Robert W. Strozier at 713.977.7000

Date: **October 7, 2003**

Respectfully submitted,

Robert W. Strozier, Reg. No. 34,024